Sensory feedback signal derivation from afferent neurons

Contract No.: **NIH-NINDS-NO1-NS-3-2380**

QUARTERLY PROGRESS REPORT #5

for the period

1 December 1993 -- 28 February 1994

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Date of submission of this report: 31 March 1994

I Summary of the Overall Project

In this study we are exploring the feasibility of extracting 1) cutaneous sensory information about fingertip contact and slip, and 2) proprioceptive sensory information about wrist or finger position. We use implanted nerve cuff electrodes to record peripheral nerve activity in animal models.

Our overall **objectives** for the 3-year duration of this contract are as follows:

1. Investigate, in cadaver material, implantation sites for nerve cuff electrodes from which cutaneous and proprioceptive information relevant to the human fingers, hand and forearm could be recorded.
2. Select a suitable animal preparation in which human nerve dimensions and electrode placement sites can be modeled and tested, with eventual human prosthetic applications in mind.
3. Fabricate nerve cuff electrodes suitable for these purposes, and subcontract the fabrication of nerve cuff electrodes of an alternate design.
4. Investigate the extraction of information about contact and slip from chronically recorded nerve activity using these animal models and electrodes. Specifically,
   a. Devise recording, processing and detection methods to detect contact and slip from recorded neural activity in a restrained animal;
   b. Modify these methods as needed to function in an unrestrained animal and in the presence of functional electrical stimulation (FES);
   c. Record activity for at least 6 months and track changes in neural responses over this time.
5. Supply material for histopathological examination from cuffed nerves and contralateral controls, from chronically implanted animals.
6. Investigate the possibility of extracting information about muscle force and limb position from chronically recorded neural activity.
7. Cooperate with other investigators of the Neural Prosthesis Program by collaboration and sharing of experimental findings.

II. Summary of our Progress in the First Year

In the first quarter we completed objective 1 and made progress toward objectives 2 and 3. In three human cadaver arms, we found appropriate implantation sites for nerve cuff electrodes from which cutaneous and proprioceptive information relevant to the human fingers, hand and forearm could be recorded. We selected the cat forelimb as the animal preparation in which human nerve dimensions and electrode placement sites are being modeled and tested. We investigated the details of the innervation of the paw and the forelimb musculature in three cats, identified several possible implantation sites, and started to design cuff electrodes suitable for these purposes.

In the second quarter we built 38 nerve cuff electrodes in assorted sizes, suitable for implantation on four nerves in the left forelimb of cats: the proximal median nerve, proximal ulnar nerve, distal median nerve, and distal ulnar nerve (objective 3). We implanted four cuffs in each of three cats, and began to follow the cuff impedance and compound action potential (CAP) properties periodically (objective 4c). We also started to design a forelimb reaching task and the hardware required to extract information about contact and slip from chronically recorded nerve activity (objective 4a, 4b).

In the third quarter we built 22 additional nerve cuffs, completing objective 3 for Year One. We implanted four cuffs in each of 5 additional cats, completing a series of 8 cats implanted in the first year. We continued to monitor cuff impedance and compound action potential (CAP) properties periodically (objective 4c) in all 8 cats. The first cat in the series was terminated prematurely at 101 days following device failure. We refined the design of the forelimb reaching task, and started the hardware design (objective 4a,b). We started to obtain the equipment required for in-house histopathological examination of cuffed nerves and contralateral control nerves (objective 5).

In the fourth quarter we continued to monitor the state of the nerves by measuring cuff impedances and compound action potentials (CAP) periodically in seven implanted cats (objective 4c). Several problems relating to long-term implantation of devices have been encountered and are being analyzed. We carried out post-mortem examination of one cat, and based on these findings we are considering some improvements in nerve cuff design (objective 3). Seven Year One cats have been trained with a passive forelimb 2-D manipulator (objective 4a,b), and the 2-D servomotor forelimb reaching task hardware has been re-designed and is being pre-tested for use with the Year Two cats. A histopathological protocol has been developed to investigate the condition of the nerves and implanted devices in the seven remaining Year 1 cats (objective 5). Finally, developments with a sub-contractor have resulted in a change in direction in nerve cuff development (objectives 3, 7).

III. Summary of Progress in the Fifth Quarter

In the fifth quarter we completed monitoring the Year One series of chronically implanted cats for 6 months (objective 4c). During a final acute surgery, nerve samples were taken from 5 cats for histological examination (objective 5). The average normalized CAP data from 9 nerves followed for 180 days was stable in both amplitude and conduction time. A number of CAP recordings were ended prematurely due cuff wire breakage. We performed a study of the distribution of cutaneous field innervation of the paw from the Ulnar and Median nerves in the cat. In preparation for the Year Two series of implants, we selected 4 candidate muscles in the cat forelimb to retrieve proprioceptive information during movement (objective 6). A discussion of the candidate muscle function and innervation is included in this report.

Details of Progress in the Fifth Quarter

A. Summary of Year One data

During the fifth quarter we completed monitoring cats NIH 2 to NIH 8 of the Year One series. Table 1 presents a summary of the Year One data, including the total days implanted for each cat, any observed mechanical problems with the implanted cuffs, and an evaluation of the nerve CAPs on the last recording day. The final nerve CAP amplitudes are reported as a percentage of the original CAP amplitudes recorded on day 0, giving an objective evaluation of the CAP stability and the nerve-cuff integrity. Proximal nerve CAP amplitudes (not reported) displayed much more variation during the implant period, due to shorter cuff lengths and the fact that stimulation of the distal cuff only stimulates a percentage of the proximal nerve fibres, making the proximal CAP smaller and more subject to changes in the nerve-cuff recording environment.

Table 1: Summary of Year One data

Subject	Total Days implanted	Problems with Implanted Cuffs		Final Distal Nerve CAP Amplitude			
		Ulnar	Median	Ulnar		Median	
				% day 0,	last day	% day 0,	last day
NIH 1	101	Wires broken after day 63	Cuff leads were too short. Cuffs removed on day 7	51%,	63	N/A	
NIH 2	212			73%,	212	90%,	212
NIH 3	202			117%,	202	24%,	202
NIH 4	189		Wires broken after day 75	71%,	189	100%,	29
NIH 5	203	Wires broken on day 135	Wires broken on day 182	131%,	132	100%,	160
NIH 6	190			84%,	190	56%,	190
NIH 7	204	Wires broken on day 151	Wires broken on day 39, cuffs removed on day 71	90%,	142	173%,	33
NIH 8	180			5%,	180	14%,	94

A total of 9 nerves out of the 15 implanted (60%; the Median nerve cuffs of NIH 1 were removed on day 7 and are not included in the data set) reached the milestone of 6 months of successful monitoring. The average duration of successful implants was 193 days, and the average distal nerve CAP amplitude on the final day of recording was 69% of the average day 0 amplitude.

On 5 nerves, the cuff wires were snagged and broken prior to day 180. The Median nerve of NIH 5 was considered a success in spite of wire breakage after day 180, given the stability of the CAP amplitude up to day 160. The only nerve that showed a severe decline in CAP amplitude that could not be attributed to a device problem was the Median nerve on NIH 8. A subclinical infection affecting the distal portions of both nerves is thought to be the cause for the decline in signal amplitude. A discussion of chronic implant problems observed in Year One and possible solutions to be implemented in Year Two can be found in Progress Report #4.

Figure 1 represents the average amplitude of the distal Ulnar and Median nerve CAPs over the implantation period of 180 days. Nine nerve recordings from 6 cats have been normalized at day 0, and interpolated to sample the data at intervals of 30 days to compare data from different cats. The Median nerve CAP data from NIH 5 has been extrapolated to day 180 for comparative purposes. Figure 2 shows that the average distal Ulnar and Median CAPs increases to about 125% at day 90 and then decreases back to approximately 100% of the day 0 amplitude at day 180. Error bars of ± 1 SD show an envelope with a maximum near the day 90 that tapers down towards day 180. In summary, the average amplitude of nine distal nerve CAP recordings was quite stable although the standard deviation was fairly large due to differences in locations and dimensions of the cuffs.

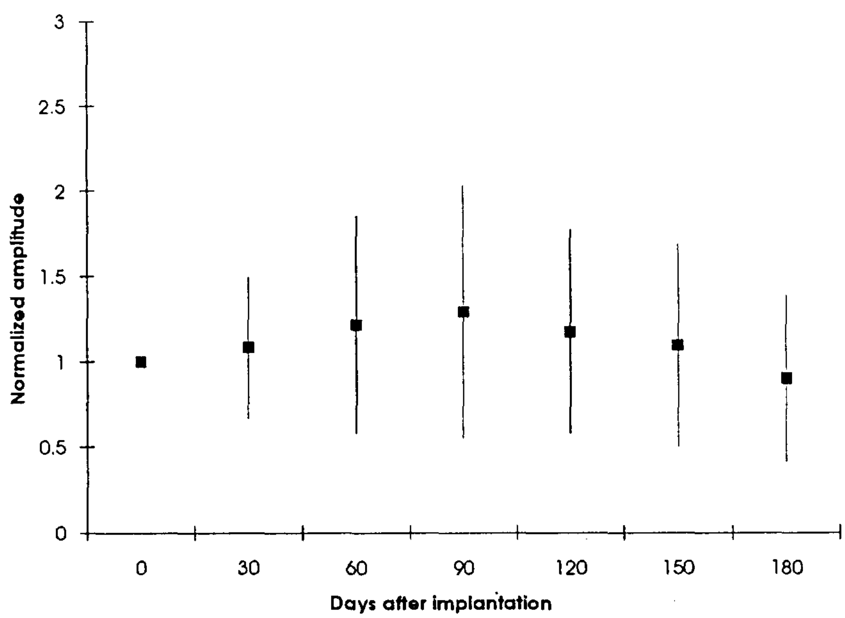

Figure 1: Average peak-peak amplitude of distal Ulnar and Median CAP ± 1 SD
(normalized at day 0; n = 9; cats 2,3,4,5,6,8)

Figure 2 portrays the average time to the first positive peak of the distal nerve CAPs. Again, the data for each cat has been normalized to day 0 and interpolated to sample the data at 30 day intervals. Normalization of the data accounts for variation in conduction times due to variation in intercuff distance from cat to cat. The average time to first peak was stable, with a slight decrease around day 90 which is consistent with the corresponding increase in average CAP amplitude according to tripolar nerve cuff recording theory (Hoffer, 1990). Standard deviation bars show that the normalized conduction times and velocities of the largest axons in the cuffed nerves were reasonably stable for all of the nerves.

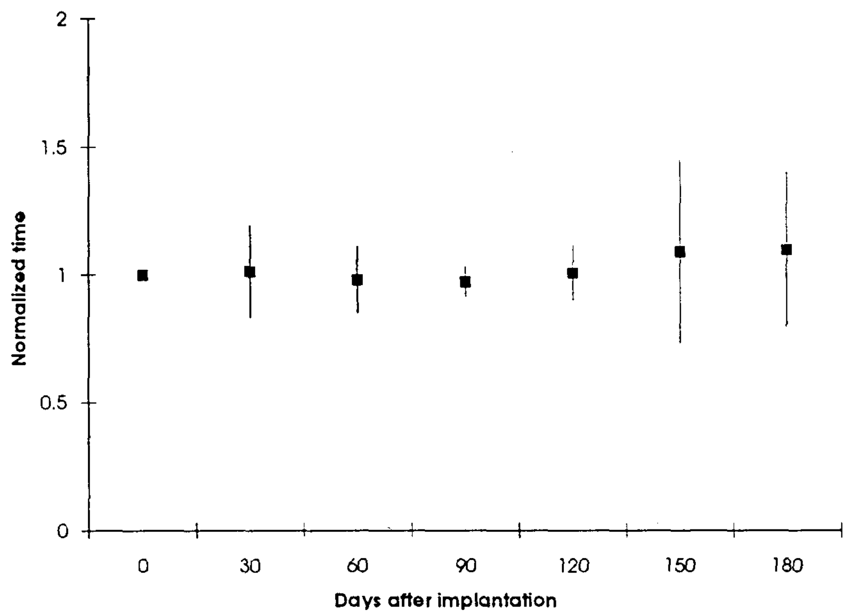

Figure 2: Average time to first positive peak of distal Ulnar and Median CAP ± 1 SD (normalized at day 0; n = 9; cats 2,3,4,5,6,8)

B. Histolopathological examination of Year One cats

The final acute surgery was performed under deep anaesthesia, in which the implantation sites were visually inspected. Connective tissue build-up around implanted devices, nerve-cuff integrity, and any signs of tissue reaction or infection were noted. Nerve samples were taken from the implanted and contralateral control limbs of five cats (NIH 2, 3, 4, 6, and 8) that had provided continuous neural recordings for greater than six months (objectives 4c and 5). Histological examination of the nerve samples will provide further information concerning the viability of chronic nerve cuff implantation.

The nerve samples are currently stored in Karnovsky's Fixative, and we are preparing to initiate a detailed histological study of the tissues.

C. Distribution of cutaneous field innervation between the Ulnar and Median nerves in the cat

We periodically monitored the innervation of cutaneous fields of the paw by the Ulnar and Median nerves in the cat forelimb. Under anaesthesia, each digit of the paw was mechanically stimulated and the resulting cutaneous afferent signals on each nerve were played through a loudspeaker and compared to determine cutaneous fields and innervation.

Our investigations have resulted in the following observations. Normally, digit I (thumb) is innervated by both the Median and Ulnar nerves while digits II and III are innervated by the Median nerve exclusively. Digit IV is also innervated by both nerves while digit V is exclusively innervated by the Ulnar nerve. The pattern of innervation of the cutaneous fields showed some variation from cat to cat, depending on the type and degree of mechanical stimulation implemented.

We also developed a method of electrically stimulating the small nerve branches running along each toe. A variation of a circumferential nerve cuff utilizing a clip to ensure contact with the pad was used to encircle the toe and apply stimulation current to the glabrous skin of the pad. Using biphasic constant current pulses to supramaximally stimulate the fibres, we found that the thresholds of stimulation were in the order of 3 to 5 mA. CAPs were recorded by the distal cuffs on the Ulnar and Median nerves, amplified, filtered, and averaged to clearly define the cutaneous innervation of each toe arising from each nerve.

Figure 3 presents the stimulation technique with digit II being stimulated by the modified nerve cuff. The five pairs of traces represent the CAPs recorded by the distal Median and Ulnar nerve cuffs when stimulating the cutaneous fibres in each toe separately. The top trace in each set is the Ulnar nerve CAP, and the bottom trace is the Median nerve CAP. The five sets clearly show the normal innervation of the toes by the two nerves, with the exception of the minimal innervation of digit I by the Ulnar nerve. The variation in conduction times to CAP onset correspond with the physical distance between the stimulated pad and the recording cuffs. Electrical stimulation of the toe afferent fibres was more controllable and reproducible than direct mechanical stimulation of the paw.

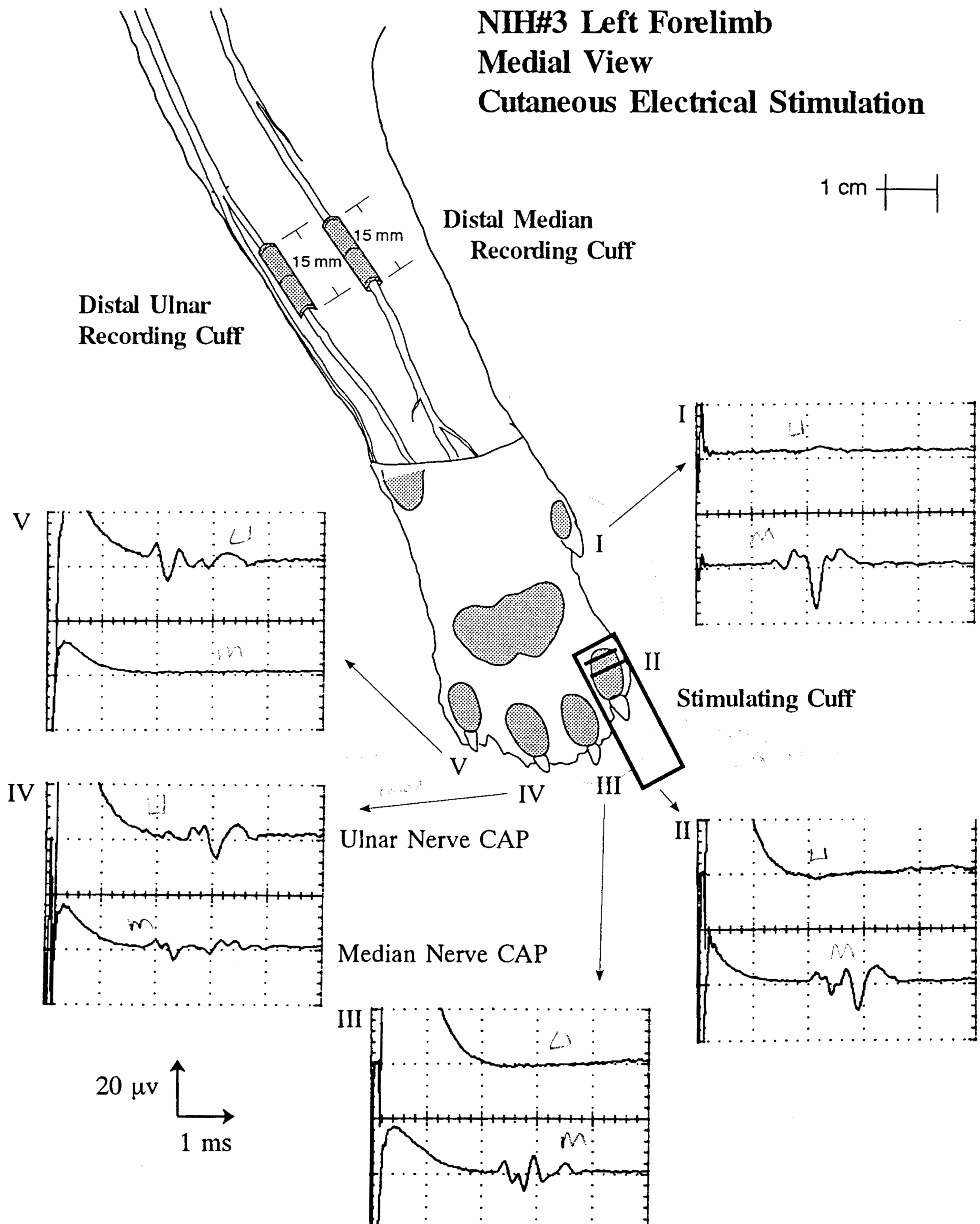

Figure 3: Cutaneous electrical stimulation of the paw

D. Year Two target muscles in the cat forelimb

We have identified four muscles in the cat forelimb as potential targets for instrumentation in the Year Two series of implants. By instrumenting nerves to individual muscles, we hope to retrieve proprioceptive afferent information concerning muscle length and limb position during active movements in the awake cat (objectives 4a, b, c). The criteria for the candidate muscles include muscle function during movement, availability of an antagonist muscle for implantation, and surgical accessibility of both muscle and muscle nerve for instrumention. Table 2 presents the muscle names, abbreviations, insertion points and functions of the candidate muscles.

Table 2: Year Two target muscles in the cat forelimb

Muscle	Abbr.	Insertion Point and Function
Flexor Carpi Ulnaris, 1st head	FCU	insertion on ulnar portion of wrist flexes and adducts paw
Extensor Carpi Ulnaris	ECU	insertion on V metacarpal extends and adducts paw
Flexor Digitorum Profundus, 5th head	FDP	insertion on tendon common to all digits flexes all digits of the paw
Abductor Pollicis Longus	APL	insertion on I digit (thumb) abducts I digit and wrist

Two sets of antagonist pairs have been identified: 1) Flexor Carpi Ulnaris, 1st head (FCU) and Extensor Carpi Ulnaris (ECU), and 2) Flexor Digitorum Profundus, 5th head (FDP) and Abductor Pollicis Longus (APL). Figures 4 and 5 illustrate the locations of the four candidate muscles in relation to the musculature of the forelimb.

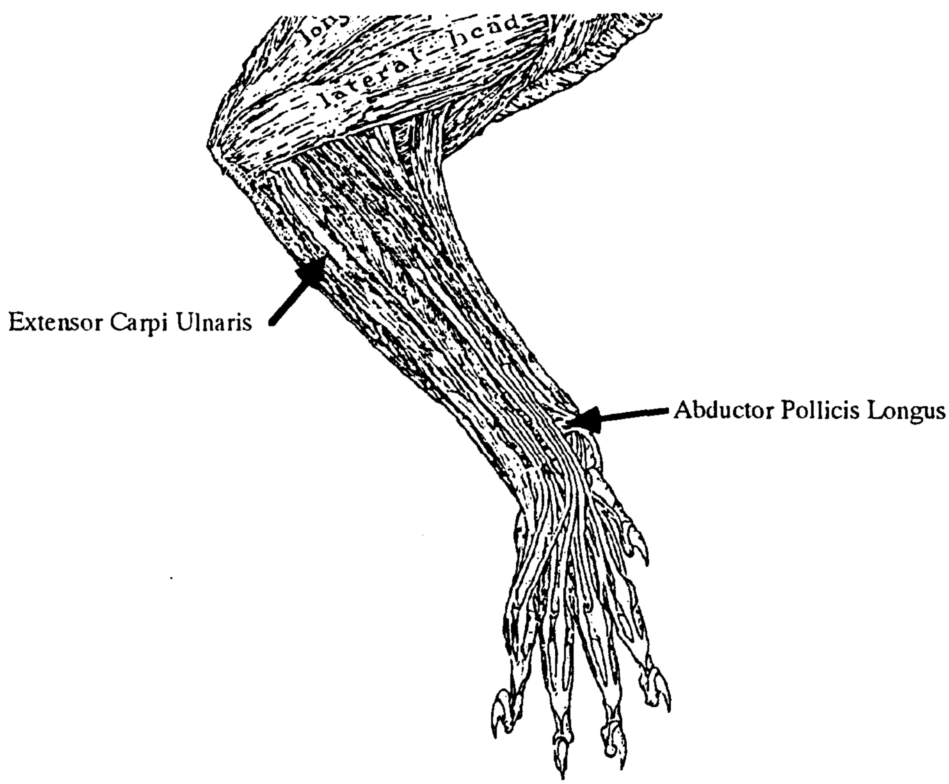

Figure 4: Lateral view of cat right forelimb (Crouch, 1969)

The FCU-ECU pair are expected to be actively involved in flexion-extension movements of the paw, and instrumenting nerves to these muscles with recording cuffs will provide neural information regarding wrist flexion and extension, as well as wrist adduction. Both the FCU and ECU are superficial muscles and should be relatively easy to instrument with EMG and cuff electrodes.

The FDP-APL form a less specific antagonistic pair. The 5th head of the FDP is a relatively deep flexor muscle and has a large tendon which inserts on all five digits of the paw. Instrumentation of the FDP 5th head muscle nerve will provide general information concerning wrist flexion and extension during forelimb movements. The APL is a deep extensor muscle whose tendon crosses over the radial side of the wrist and inserts on the I digit. The APL extends and abducts the I digit and wrist.

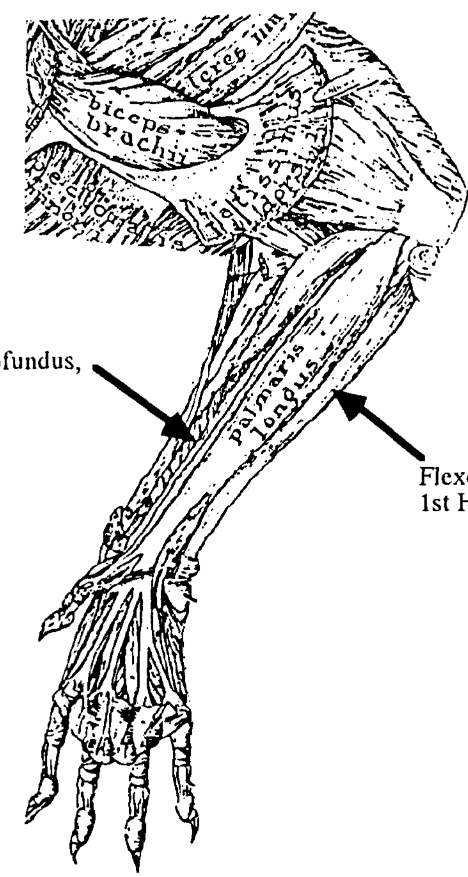

Figure 5: Medial view of cat right forelimb (Crouch, 1969)

C. Year Two target muscle nerve dimensions

Anatomical studies of cat cadaver forelimbs have resulted in consistent innervation data of the four candidate muscles discussed in the previous section. These muscle nerves are much smaller on average than the cutaneous nerves instrumented in the Year One series of implants, and thus will require very fine nerve cuffs and careful layout to avoid mechanical trauma to the nerve and successfully record the neural signal while blocking out EMG from the surrounding muscles. Table 3 presents the results of the cadaver studies with nerve diameter and free length ranges and averages for the four candidate muscles.

Table 3: Summary of muscle nerve dimensions

Muscle	n	Extreme nerve diameter range mm.	Mean nerve diameter ± 1.SD mm	Extreme nerve free length range mm.	Mean nerve free length ± 1.SD. mm.
FDP	6	0.4 - 1.0	0.6 ± 0.2	8 - 20	13 ± 4
FCU	8	0.3 - 0.7	0.5 ± 0.1	7 - 17	11 ± 3
APL	6	0.4 - 0.8	0.6 ± 0.1	10 - 16	13 ± 2
ECU	7	0.5 - 1.5	0.9± 0.4	7 - 20	10 ± 4

V. Plans for Sixth Quarter

In the sixth quarter we intend to:

1. initiate histopathological examination of Year One cats (objective 5)
2. train Year Two cats on treadmill and forelimb task (objective 4a)
3. begin Year Two implant series
4. begin monitoring status of Year Two implanted nerves and electrodes (objective 4)
5. finalize design of smaller cuffs for proprioceptive nerves (objective 3)
6. complete the construction of hardware for the reaching task (objective 4a,b)

VI. References

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Hoffer, J.A. Techniques to record spinal cord, peripheral nerve and muscle activity in freely moving animals. *In:* Neurophysiological Techniques: Applications to Neural Systems. NEUROMETHODS, Vol. 15. *Edited by* A.A. Boulton, G.B. Baker and C.H. Vanderwolf. Humana Press, Clifton, N.J. pp. 65-145, 1990.